Role of Postoperative Radiotherapy in Nonlocalized Thymoma

Propensity-Matched Analysis of Surveillance, Epidemiology, and End Results Database

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Introduction: Because of a lack of randomized trials, the role of postoperative radiotherapy (PORT) in thymomas has not been established. This study evaluated the prognostic impact of the adjuvant treatment in surgically resected nonlocalized thymomas.

Methods: Patients diagnosed between 2000 and 2010 were identified from the Surveillance, Epidemiology, and End Results database (1973–2011 registry). Cases with localized or organ-confined tumors were not included. Propensity-matched analysis was conducted considering baseline characteristics.

Results: A total of 529 patients were identified. The median age was 57 years (range, 18–86), and 345 (65%) patients received PORT. Before and after propensity score matching, overall survival (OS; $p = 0.018$ and 0.008, respectively) and disease-specific survival (DSS; $p = 0.007$ and 0.008, respectively) were better in the PORT group. In multivariate analyses of the matched population, no receipt of PORT induced poorer OS (hazard ratio [HR], 1.98; 95% confidence interval [CI], 1.27–3.09) and DSS (HR, 2.64; 95% CI, 1.32–5.29). Primary tumor extensions of adjacent organs or structures and further contiguous extensions also resulted in worse outcomes ($p < 0.001$ and equal to 0.039 for OS; $p = 0.006$ and 0.009 for DSS, respectively). In the subgroup analyses, PORT was associated with favorable OS in stages III and IV ($p = 0.049$ and 0.012, respectively) and DSS in stage III ($p = 0.005$).

Conclusion: Regarding the independent prognostic significance of PORT, this population-based analysis demonstrates the survival benefits of PORT in relation to nonlocalized thymomas. We recommend consideration of PORT in the poor prognostic subset of stages III to IV in the contemporary era.

Key Words: Thymoma, Adjuvant radiotherapy, Survival analysis, SEER program, Propensity score, Masaoka stages III and IV.

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Thymomas are a common primary malignancy in the anterior mediastinum.[1] According to a nation-wide report, the incidence of thymoma is approximately 0.15 per 100,000 person-years in the United States.[2] Although the diagnosis and histologic features of thymomas and thymic carcinomas were previously confused, their differential schema were published in 1999 by the World Health Organization (WHO) Consensus Committee.[3] Masaoka staging was defined based on the primary tumor extension and the degree of involvement of the surrounding organs.[4] The classification of stages I to IV is related to the natural course of local invasiveness, accounting for its common use in clinical practices.

For the curative management of thymomas, maximal tumor resection is the mainstay treatment. The patterns of failure have mostly involved locoregional recurrences in accordance with recurred tumors in the mediastinum or extramediastinal pleura.[5] Though postoperative radiotherapy (PORT) has been considered for enhancing postsurgical tumor control, there have been few randomized controlled trials to assess the role of PORT because of its rarity and slow growth. To date, the survival benefits of PORT have been controversial, and receipt of the adjuvant treatment is still dependent on institutional policy. PORT is not recommended in organ-confined stage I disease because of its excellent prognosis.[6,7] In stages II to IV, treatment indications are still unknown, and PORT is usually recommended in incompletely resected tumors.[8,9] Concerning complete resection, several previous studies have reported a lack of association between PORT and patients' mortality.[10–12]

A few years ago, several investigations evaluated the role of PORT in thymomas based on the Surveillance, Epidemiology, and End Results (SEER) database.[13–16] Although they obtained survival outcomes in favor of the receipt of PORT, its independent statistical significance was not clearly reported. This study explored the prognostic impact of PORT in patients with stages IIB to IV thymomas using the SEER registry. We excluded the stage I disease considering its long-term survival and limited role of PORT expected. Stage IIA with microscopic transcapsular invasion could not be differentiated from stage I in the nation-wide data. Therefore, based on the SEER database, the present analysis defined "nonlocalized" tumors as the Masaoka stages IIB to IV.

To minimize the selection bias in the receipt of PORT, propensity score matching was conducted, and the distribution of baseline clinicopathologic variables was balanced. This population-based study can provide insight into the therapeutic role of PORT with modern radiotherapy (RT) techniques.

PATIENTS AND METHODS

Patients

This study used the SEER 18-Registry (1973–2011 data set) of the National Cancer Institute. SEER is an authoritative nation-wide cancer database in the United States.[17] We used SEER*Stat software (version 8.1.5; National Institutes of Health, Bethesda, MD) to extract the cases from the database.

Cases with the primary site of the thymus were obtained using the variable of "primary site labeled," and the histology of thymomas were determined by the International Classification of Diseases codes (8580, 8581, 8582, 8583, 8584, and 8585) with the behavior code "/3," indicating thymomas of the type not otherwise specified, A, AB, B1, B2, and B3, respectively. Patients aged 18 years or more and diagnosed from 2000 to 2010 were selected. Patients who had undergone primary surgical resection with or without PORT were identified using the variables of "radiation sequence with surgery," "radiation," and "reason no cancer-directed surgery." Regarding the extent of surgical tumor resection, radical, total, simple or partial, and debulking surgery codes were selected. Simple/partial or total surgical resection was determined based on the extent of macroscopic surgical removal, and debulking surgery was coded in cases with the surgery stated to be "debulking." The SEER registry defined radical surgery as partial or total removal of the primary site with an en bloc resection (partial or total removal) of other organs. Patients with a survival time of 3 months or less were excluded in the analysis to rule out perioperative mortality.

Because patients' stage information was unknown in SEER, the Masaoka stage was inferred from several existing variables, such as primary tumor extension, lymph node status, and SEER historic stage. The tumor extent codes "localized or organ-confined," "adjacent connective tissue," "adjacent organs or structures in the mediastinum," and "further contiguous extension" were in accordance with the local tumor invasiveness of stages I to IIA, IIB, III, and IV, respectively.[13] Positive lymph node disease or the "distant" status of the SEER stage was considered stage IV. However, the stages I and IIA or IVA and IVB could not be differentiated based on the SEER data. Nonlocalized thymomas were classified as stages IIB, III, or IV.

Propensity Score Matching

Because the patients were not randomized in the database, selection bias from baseline characteristics could influence the receipt of PORT. A propensity score is defined as the probability being assigned to PORT or non-PORT groups given the clinicopathologic characteristics.[18] In the calculation of the propensity scores, the nonparsimonious logistic regression model was used considering predefined baseline covariates, including age at diagnosis, gender, race, marital status, other malignancies, tumor extent, lymph node status, and extent of surgery.[19] Patients treated with PORT were matched to the others based on the calculated scores with an algorithm of the nearest neighbor and 1:1 matching without a specific caliper width or replacement.[20]

Statistical Analysis

The clinicopathologic variables were categorized. In this study, overall survival (OS) and disease-specific survival (DSS) were the primary and secondary outcomes of interest, respectively. The survival time was defined as the time interval between the diagnosis of thymomas and deaths. Kaplan–Meier analyses were conducted to estimate the survival outcomes before and after propensity score matching. Using a log-rank test, the survival differences between the PORT and non-PORT groups were compared. In the multivariate analyses of the matched population, the Cox proportional hazards model was used. Related clinicopathologic factors with p values of less than 0.1 in the univariate analyses were adjusted. Statistical significances were declared when the two-sided p values were less than 0.05. All of the statistical analyses were performed with IBM SPSS Statistics 22.0 (IBM, Armonk, NY) and R version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

A total of 529 patients with thymomas were identified. The baseline patient characteristics are listed in Table 1. The median age was 57 years (range, 18–86), and 280 (53%) patients were men. White patients comprised 67% of the entire population, and 331 (62%) patients were married. Sixty-eight (13%) patients were diagnosed with other malignancies. Primary tumors extending into the adjacent connective tissue, adjacent organs or structures, and with further contiguous extensions were observed in 179 (34%), 281 (53%), and 69 (13%) patients, respectively. The median tumor size was 6.5 cm (range, 0.3–23), and 121 (23%) patients had tumors of WHO histological classification type B3. Positive regional lymph node status was reported in 75 (14%) patients. Concerning the extent of surgical resection, 165 (31%), 220 (41%), 120 (23%), and 24 (5%) patients underwent radical surgery, total resection, simple or partial resection, and debulking surgery, respectively. Postoperative radiation was performed on 345 (65%) patients.

Survival Outcomes Before Propensity Score Matching

In the unmatched population (n = 529), 120 patients had died at the time of analysis. The 5-year and 7-year rates of OS were 81.8% and 72.5%, respectively. There were 50 death events caused by the diagnosis of thymomas, and the 5-year and 7-year rates of DSS were 91.5% and 87.6%, respectively.

Kaplan–Meier curves of OS and DSS according to the receipt of PORT are represented in Figure 1. For both OS and DSS, there were significant differences between the PORT and non-PORT groups in favor of the adjuvant treatment. The 7-year OS rates of the PORT and non-PORT groups were 75.8% and 66.1% (p = 0.018), respectively. The 7-year DSS rates of the PORT and non-PORT groups were 90.9% and 81.2% (p = 0.007), respectively.

TABLE 1. Baseline Characteristics of Surgically Resected Nonlocalized Thymoma Patients (N = 529)

Characteristics	N (%)
Age (yrs)	
Median (range)	57 (18–86)
<40	82 (16)
40–49	99 (19)
50–59	118 (22)
60–69	124 (23)
≥70	106 (20)
Gender	
Men	280 (53)
Women	249 (47)
Race	
White	356 (67)
Black	79 (15)
Others	91 (17)
Unknown	3 (1)
Marital status	
Married	331 (62)
Not married	183 (35)
Unknown	15 (3)
Other malignancy	
No	461 (87)
Yes	68 (13)
Tumor extent	
Adjacent connective tissue	179 (34)
Adjacent organs or structures	281 (53)
Further contiguous extension	69 (13)
Tumor size (cm)	
Median (range)	6.5 (0.3–23)
<6.5	212 (40)
≥6.5	252 (48)
Unknown	65 (12)
WHO classification	
Not otherwise specified	142 (27)
Type A	40 (7)
Type AB	79 (15)
Type B1	77 (15)
Type B2	70 (13)
Type B3	121 (23)
LN status	
Regional LN (−)	422 (80)
Regional LN (+) or LNs, NOS	75 (14)
Unknown	32 (6)
Extent of surgery	
Radical surgery	165 (31)
Total resection	220 (41)
Simple or partial resection	120 (23)
Debulking surgery	24 (5)
Adjuvant external beam radiotherapy	
Yes	345 (65)
No	184 (35)

WHO, World Health Organization; LN, lymph node; NOS, not otherwise specified.

Prognostic Significance After Propensity Score Matching

The matching process resulted in a balanced study population including PORT (n = 184) and non-PORT (n = 184) groups. Table 2 lists the detailed balances before and after propensity score matching. The absolute values of standardized differences were reduced in all covariates, suggesting that potential selection bias in the receipt of PORT was minimized.

Figure 2 shows the Kaplan–Meier curves of OS and DSS in the matched population. The 7-year OS rates of the PORT and non-PORT groups were 78.5% and 66.1% ($p = 0.008$), respectively. For DSS, the 7-year rates of the two groups were 92.1% and 81.2% ($p = 0.008$), respectively.

In the univariate analyses, the survival differences were assessed according to age at diagnosis (< 57 or ≥ 57 years), gender (men or women), race (white or other), marital status (married or not married), other malignancies (no or yes), primary tumor extension (adjacent connective tissue, organs and structures, or further contiguous extension), tumor size (<6.5 or ≥6.5 cm), WHO histological classification (nontype B3 or type B3), regional lymph node status (negative or positive), extent of surgery (radical, total, simple/partial, or debulking surgery), and the receipt of PORT (yes or no). Age ($p < 0.001$), primary tumor extension ($p = 0.004$), and PORT ($p = 0.008$) were associated factors of OS. For DSS, primary tumor extent ($p = 0.010$) and PORT ($p = 0.008$) were prognostic.

Table 3 lists the results of the multivariate survival analyses of the matched population. With the Cox proportional hazards model of OS, an age of 57 years or more (versus age of <57 years; hazard ratio [HR], 2.60; 95% confidence interval [CI], 1.62–4.17), tumor invasion into adjacent organs/structures and further contiguous extensions (versus adjacent connective tissue; HR, 2.69; 95% CI, 1.59–4.58 and HR, 2.15; 95% CI, 1.04–4.43, respectively), and no receipt of PORT (versus receipt of PORT; HR, 1.98; 95% CI, 1.27–3.09) were poor prognostic factors. For DSS, tumor invasion into adjacent organs/structures and further contiguous extensions (versus adjacent connective tissue; HR, 3.55; 95% CI, 1.44–8.73 and HR, 4.15; 95% CI, 1.44–11.96, respectively) and no receipt of PORT (versus receipt of PORT; HR, 2.64; 95% CI, 1.32–5.29) were associated with shorter survival time.

Subgroup Analysis

Figure 3 represents OS and DSS curves in the subgroup analyses of the Masaoka stages IIB to IV. In the patients with stage IIB thymomas, no survival differences were observed in either OS or DSS according to the receipt of PORT ($p = 0.738$ and 0.405, respectively). However, PORT resulted in better OS and DSS in stage III ($p = 0.049$ and 0.012, respectively). Superior OS was also observed for PORT in stage IV ($p = 0.005$), but DSS was not significantly different ($p = 0.139$).

DISCUSSION

There have been few randomized trials to assess the efficacy of PORT in thymomas. Because well-localized or organ-confined stage I thymoma has an excellent prognosis, the prognostic influence of PORT has been suggested to be limited in such a disease entity.[7,21–23] To evaluate potential

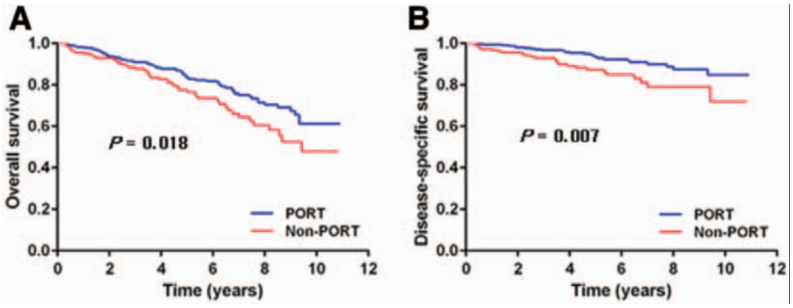

FIGURE 1. Comparison of overall survival (*A*) and disease-specific survival (*B*) according to the receipt of postoperative radiotherapy before propensity score matching. PORT, postoperative radiotherapy.

TABLE 2. Patient, Tumor, and Treatment Characteristics Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
Variables	**PORT (+) (N = 345)**	**PORT (−) (N = 184)**	**Standardized Difference**	**PORT (+) (N = 184)**	**PORT (−) (N = 184)**	**Standardized Difference**
Age (yrs)						
<40	56 (16)	26 (14)	0.116	29 (16)	26 (14)	0.050
40–49	61 (17)	38 (21)		34 (18)	38 (21)	
50–59	85 (25)	33 (18)		36 (20)	33 (18)	
60–69	85 (25)	39 (21)		46 (25)	39 (21)	
≥70	58 (17)	48 (26)		39 (21)	48 (26)	
Gender						
Men	183 (53)	97 (53)	0.007	97 (53)	97 (53)	< 0.001
Women	162 (47)	87 (47)		87 (47)	87 (47)	
Race						
White	232 (67)	124 (67)	−0.077	132 (72)	124 (67)	0.036
Black	45 (13)	34 (18)		22 (12)	34 (18)	
Others	66 (19)	25 (14)		30 (16)	25 (14)	
Unknown	2 (1)	1 (1)		0 (0)	1 (1)	
Marital status						
Married	226 (66)	105 (57)	0.174	104 (56)	105 (57)	−0.010
Not married	111 (32)	72 (39)		73 (40)	72 (39)	
Unknown	8 (2)	7 (4)		7 (4)	7 (4)	
Other malignancy						
No	296 (86)	165 (90)	−0.127	166 (90)	165 (90)	0.018
Yes	49 (14)	19 (10)		18 (10)	19 (10)	
Tumor extent						
Adjacent connective tissue	108 (31)	71 (39)	−0.108	66 (36)	71 (39)	−0.016
Adjacent organs or structures	192 (56)	89 (48)		97 (53)	89 (48)	
Further contiguous extension	45 (13)	24 (13)		21 (11)	24 (13)	
LN status						
Regional LN (−)	280 (81)	142 (77)	0.117	142 (77)	142 (77)	0.035
Regional LN (+) or LNs, NOS	48 (14)	27 (15)		31 (17)	27 (15)	
Unknown	17 (5)	15 (8)		11 (6)	15 (8)	
Extent of surgery						
Debulking surgery	19 (6)	5 (3)	−0.087	9 (5)	5 (3)	0.032
Simple/partial surgical resection	70 (20)	50 (27)		43 (23)	50 (27)	
Total surgical resection	148 (43)	72 (39)		84 (46)	72 (39)	
Radical surgery	108 (31)	57 (31)		48 (26)	57 (31)	

PORT, postoperative radiotherapy; LN, lymph node; NOS, not otherwise specified.

survival differences according to the receipt of PORT, this SEER-based analysis targeted nonlocalized tumors diagnosed and treated in the contemporary era.

Until now, several SEER-based studies have evaluated the role of PORT in thymomas.[13–16] However, this study is distinguishable in that propensity score matching was firstly

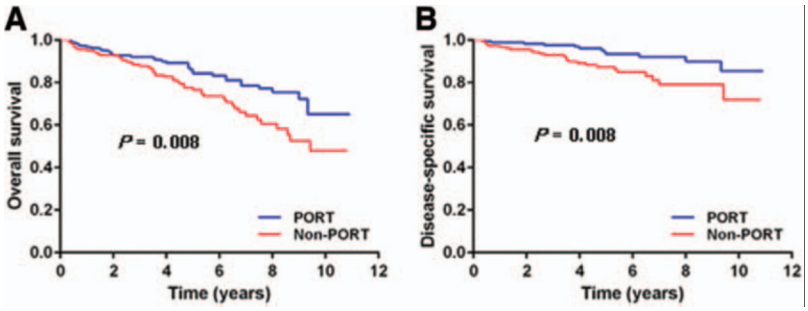

FIGURE 2. Comparison of overall survival (*A*) and disease-specific survival (*B*) according to the receipt of postoperative radiotherapy after propensity score matching. PORT, postoperative radiotherapy.

TABLE 3. Multivariate Analyses of Overall and Disease-specific Survival in the Matched Population

	Overall Survival			Disease-specific Survival		
Variables	**Hazard Ratio**	**95% CI**	***p* Value**	**Hazard Ratio**	**95% CI**	***p* Value**
Age (yrs)						
<57	Reference					
≥57	2.60	1.62–4.17	<0.001			
Tumor extent						
Adjacent connective tissue	Reference			Reference		
Adjacent organs or structures	2.69	1.59–4.58	<0.001	3.55	1.44–8.73	0.006
Further contiguous extension	2.15	1.04–4.43	0.039	4.15	1.44–11.96	0.009
PORT						
Yes	Reference			Reference		
No	1.98	1.27–3.09	0.003	2.64	1.32–5.29	0.006

CI, confidence interval; PORT, postoperative radiotherapy.

used in relation to the potential selection bias in the receipt of PORT. From the matching process with patient, tumor, and treatment-related covariates, the well-balanced PORT and non-PORT groups were obtained.[24] Because prior studies have mostly analyzed patients diagnosed before the 2000s, the present survival outcomes of patients diagnosed in the 2000s are updated results reflecting recent RT techniques. To assess patients' Masaoka stage, this study summarized the information of SEER-based variables. Nonlocalized thymomas were classified into stages IIB, III, or IV in the SEER data.

In our results, OS and DSS were longer in the PORT group both before and after the propensity score matching. Multivariate analyses of the matched patients showed the independent poor prognostic impacts of older age (≥57 years), more extensive primary tumor extensions (adjacent organs or structures and further contiguous extensions), and no receipt of PORT on OS, and the tumor extensions and PORT were also significantly associated with DSS. In the subgroup analyses according to Masaoka stage, PORT significantly improved OS in stages III to IV and DSS in stage III, whereas there were no OS and DSS differences between the PORT and non-PORT groups in stage IIB.

The need for PORT has not been established in stage II thymomas. Singhal et al[25] reported survival outcomes of 70 patients with completely resected stages I to II thymomas and failed to show PORT-induced survival differences. In a retrospective study of 62 patients with completely resected stage II tumors,[26] there was no significant difference in the proportion of recurrences either with or without PORT ($p = 0.15$). Furthermore, in a population-based investigation using the British Columbia Cancer Agency Registry, there was no difference in OS or freedom from recurrence according to the receipt of PORT.[27] In this study, the propensity-matched subgroup analyses indicated no effects of PORT on both OS and DSS in stage IIB thymomas. Considering the less invasive nature of stage IIA, which was not included in the analysis, we demonstrate that the survival advantage of PORT might not be expected in stage II thymomas.

In addition, the prognostic impact of PORT in stage III has been controversial. Weksler et al[16] analyzed 499 patients with stage III thymomas using the SEER database. No receipt of PORT resulted in a worse prognosis in DSS ($p = 0.049$) in the multivariate analysis, whereas there was no statistical significance in OS ($p = 0.493$). Although the difference in cause-specific mortality was considered notable, the PORT group included more patients with younger ages or who have undergone debulking surgery. More recently, a retrospective study of the Japanese multi-institutional database reported that PORT did not improve either OS ($p = 0.172$) or relapse-free survival ($p = 0.362$) in stage III thymomas.[12] Despite the value of the national large-scale analysis, the distributions of baseline clinicopathologic features, including age at diagnosis, tumor size, Masaoka stage, and completeness of surgery, were significantly different in the PORT and non-PORT groups. Contrary to stages II to III thymoma, in stage IV, clinical data on PORT were not sufficiently reported. Instead, the role of

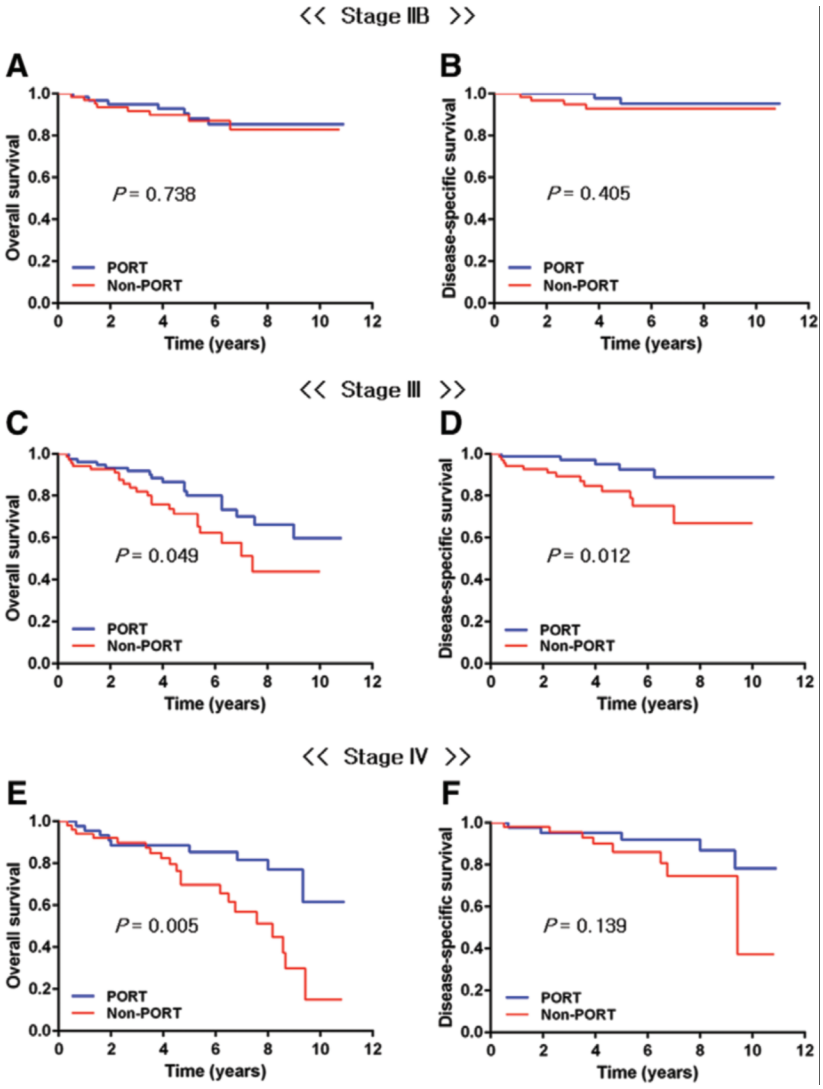

FIGURE 3. Overall survival and disease-specific survival of the stage IIB (*A* and *B*), stage III (*C* and *D*), and stage IV (*E* and *F*) with or without postoperative radiotherapy. PORT, postoperative radiotherapy.

chemotherapy as an adjuvant or neoadjuvant treatment strategy has been investigated.[28–30] Therefore, our results on the survival advantages in stages III to IV could contribute important knowledge of the clinical implications of PORT in thymomas.

Several large-scale studies have reported the survival outcomes of stages III to IV with or without PORT. Kondo and Monden[31] reported on the Japanese multi-institutional analysis, and the authors found no role of PORT in totally resected stages III and IV thymomas. However, patient selection bias cannot be excluded, because no adjuvant therapy obtained significantly better survival compared with radiochemotherapy ($p = 0.0353$). In one previous SEER analysis, PORT improved OS in a univariate analysis of stages III and IV ($p = 0.04$).[13] Although this result was compatible with our study, its statistical significance was eliminated in a multivariate analysis. Interestingly, the increasing year of diagnosis was significantly associated with improved OS (the years of 1973–1983 versus 1984–1993 versus 1994–2003). In this study, the survival benefits of PORT irrespective of other clinicopathologic factors were initially reported. We suggest that the propensity score matching and more recently diagnosed patients analyzed in this study might be attributed to the significant results. In fact, the Chinese group recently demonstrated that the three-dimensional conformal/intensity-modulated RT technique seemed to be associated with longer survival and reduced relapse rates compared with conventional RT.[32] Continued research is necessary to estimate the survival advantages of PORT in the modern era of RT.

This study has several limitations. Pathologic resection margins were not reported in the SEER database, limiting the analysis of microscopic resection margins. In addition, the registry did not include any information on patients' performance status, combined morbidity, or use of chemotherapy. With the limited surgery-related information, the detailed surgical techniques and the degree of surgical skill of each institution were not obtainable. Regarding RT methods, the total radiation dose, fraction size, extent of treatment field, and radiation techniques were not described. Because other unmeasured potential confounders in the database could not be excluded, the propensity score matching did not fully eliminate the limitations of the

retrospective design. The present analyses included patients with relatively shorter follow-up durations, and additional analyses with longer follow-ups are essential.

Although this study suggested the significant impact of RT-induced local tumor control on patients' survival outcomes, we could not assess the extent of irradiation field and its relevance to failure patterns or survival in the nation-wide population. A retrospective study recently analyzed 156 patients with stages II to IV thymomas undergoing involved field RT after surgical resection.[33] In-field failures were observed in only five patients, but out-of-field recurrences were also reported in 22 patients. These results were similar with the prior investigations,[34–36] and the authors pointed out the need of more discussions on the optimal RT fields to reduce pleural recurrences. Concerning RT-related pulmonary or cardiac toxicities, much extended irradiation fields could not be recommended in clinical practices. Nevertheless, there is the potential for the extended irradiation fields or RT dose escalation using the modern RT techniques. To improve long-term outcomes of nonlocalized thymomas, further studies to optimize RT methods are necessary.

Based on the SEER registry, this propensity-matched analysis firstly ascertained the independent survival advantages of PORT in nonlocalized thymomas. Our significant results seem markedly important in that other previous investigations have been usually inconclusive. In subgroup analyses according to Masaoka stage, better survival outcomes with PORT were verified in stages III and IV. Considering the poor prognostic impacts of no receipt of PORT and more invasive tumor extents, we suggest that the use of RT after surgical resection is recommended in patients with stages III to IV thymomas. Further investigations are necessary to identify the detailed treatment indication of PORT in nonlocalized thymomas.

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